APP #	TITLE	BUDGET REQ	FUND	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Product Type	Approach
CLINICAL APPLICATIONS												
CLIN2COVID19-11775	Evaluation and Characterization of SARS-CoV-2 Antibody in Convalescent Volunteer Plasma Donors for Potential Therapeutic Use	$749,999	**Y**	**85**	84	5	70	90	11	4	Convalescent plasma	Program to screen plasma donors and analysis of neutralizing properties of infused plasma in patients.
TRANSLATIONAL APPLICATIONS												
TRAN1COVID19-11793	COVID-19 Antiviral Therapy to Block Lung Stem Cell Injury and Associated Tissue Damage	$349,999	**N**	**80**	80	8	60	90	7	8		
TRAN1COVID19-11837	Development of Decidua Stromal Cells for the Treatment of COVID-19-induced Acute respiratory distress syndrome (ARDS) or any ARDS	$350,000	**N**	**70**	65	11	30	75	0	15		
DISCOVERY APPLICATIONS												
DISC2COVID19-11817	Stem cell-based rapid identification of SARS-CoV-2 T cell epitopes and T cell receptors for therapeutic use	$150,000	**Y**	**95**	95	3	90	100	15	0	Tool for vaccine/T cell therapy development	Use of a stem cell-based platform to identify viral epitopes and T cell receptors for vaccine and therapy development.
DISC2COVID19-11764	Identifying a lead compound for COVID19 using high throughput screening with lung stem cell organoids	$149,998	**Y**	**85**	83	5	70	86	11	4	Small molecule drug	Screen small molecule drug library using lung organoid model.
DISC2COVID19-11779	Mesenchymal stem cell derived exosome repression of SARS-CoV-2	$150,000	**N**	**80**	77	10	60	87	4	11		
DISC2COVID19-11724	Rational Design of a SARS-CoV-2 Vaccine	$149,999	**N**	**75**	73	8	60	95	1	14		
DISC2COVID19-11729	Preclinical Development of An HSC-Engineered Off-The-Shelf iNKT Cell Therapy for COVID-19	$149,998	**N**	**70**	67	6	55	75	0	14		
DISC2COVID19-11763	Development of TMPRSS2 antibody as an antiviral treatment for SARS-CoV-2 (COVID-19)	$150,000	**N**	**65**	68	6	65	85	1	14		
DISC2COVID19-11759	Therapeutic strategy for COVID 19 associated acute cardiac injury using hPSC modeling approaches	$149,998	**N**	**-**	-	-	-	-	0	15		
DISC2COVID19-11755	Nebulized mesenchymal stem cell therapy for COVID-19 patients	$149,993	**N**	**-**	-	-	-	-	0	15		

Application #	CLIN2COVID19-11775
Title (as written by the applicant)	Evaluation and Characterization of SARS-CoV-2 Antibody in Convalescent Volunteer Plasma Donors for Potential Therapeutic Use
Therapeutic Candidate (as written by the applicant)	COVID-19 convalescent plasma (CCP)
Indication (as written by the applicant)	Treatment of severe COVID-19 infection
Unmet Medical Need (as written by the applicant)	There currently is no approved treatment of COVID-19 infection, and CCP is available now to use in severely ill patients.
Major Proposed Activities (as written by the applicant)	• Development of a screening program in California to identify potential CCP donors • Characterization of the titer and neutralizing properties of anti-SARS-CoV-2 antibodies in CCP • Prospective analysis in CCP recipients based on the clinical course of the disease and the CCP immunogenic profile
Funds Requested	$749,999
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

ASSESSMENT OF VITAL RESEARCH OPPORTUNITY

For projects that are not stem cell-based, the GWG must determine by a 2/3 majority vote whether they believe the project represents a vital research opportunity to permit funding. The vote tally is presented below.

GWG Vital Research Opportunity Vote:

Yes	15
No	4
Abstain	1

SCORING DATA

Final Score: 85

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	84
Median	85
Standard Deviation	5
Highest	90
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	4

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• There is an unmet need for COVID-19-specific treatments other than supportive care, and convalescent plasma, if proven to be efficacious, could help meet that need and could improve the standard of care for patients.

	• The project could provide advances in fundamental knowledge about antibodies in CCP, and may provide an important understanding of types of antibodies formed after COVID-19 infection. • Convalescent sera has enormous potential for the development of new antibody based therapeutic. • Even though there is much work at other labs to characterize antibodies, there is so much we don't know about COVID-19. Any effort that can help to elucidate the effect of the virus on clinical antibody profiles will add to our understanding. • This will help develop a new screening tool for the California public-health arsenal by identifying what patient and CCP donor factors predict clinical benefit. • While this study would generate valuable pre-clinical serologic data, the overall approach is not likely to prove or suggest that CCP should be added to standard of care in COVID-19 positive patients because 1) correlating antibody levels to outcome is impossible because nothing is planned about monitoring the volume of CCP given, which is currently suggested to be between 200 and 400 mL 2) antivirals are likely to emerge and affect standard of care before CCP data is fully characterized and 3) changes to standard of care would likely require a randomized controlled trial, which is out of the scope of this proposal.
No: 3	• This proposal is part of an important global effort to understand the antibody response to SARS-CoV-2 infection. The exploratory plans to better characterize CCP using peptide libraries, standard Spike protein Antibody testing (IgM/IgG), and two functional assays (one still in development apparently) are exciting, even if they will likely duplicate work being performed in many other locations. The most compelling component of this application is the promise of clinical correlation. However, the lack of a credible plan for correlation with clinical data is a concern. This project has great potential as a kind of pseudo-randomized experiment (using the donor CCP characteristics as an unbiased exposure), but the proposal lacks any evidence that such will be performed. Instead, it seems like this will be an exploration of CCP immunologically with limited clinical application. • The study is exploratory and not well thought out for actually developing a therapy that will impact the disease in a reasonable level of time.
GWG Votes	Is the rationale sound?
Yes: 13	• The rationale is very clear and compelling. • The rationale is a major strength. It would be good to get more molecular detail about CCP. • The rationale is sound, but the details leave the impression that this team may not be equipped to see such a project to success. • A major barrier to the use of CCP is determining how to evaluate potency. This proposal has a sound approach to measuring and characterizing the antibody response in donors, specifically evaluating the neutralizing antibody response, which is predicted to be the mechanism for passively transferring therapeutic benefit in CCP. Since the use of CCP is occurring anyway, better characterization of CCP characteristics would significantly add to the scientific understanding of CCP. • Convalescent plasma is a promising therapy for severely ill COVID-19 patients. Characterization of antibody types and function present in sera is an important aspect of the proposed work. • The idea to measure antibody type and levels as well as examine any antibody-dependent enhancement of infection have not been currently investigated. These will be important to understand and defeat the virus. • The volume of plasma transfused is not part of the case report form in this proposal, and the FDA is recommending 200 to 400 mL of plasma. Not recording the dose means that the amount of antibodies given to patient on a per weight basis cannot be determined. A very high-titer, low volume product and a low-titer, high volume product might be equivalent in actual antibody dose. Therefore to correlate antibody characteristics with outcome, the dose needs to be captured. • Opportunity to leverage Alpha Clinics.
No: 2	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 7	• The applicants provide a clear presentation of how they will systematically characterize antibodies formed after COVID-19 infection. • This study is designed to support preclinical projects by characterizing donor convalescent plasma including antibody levels and neutralizing characteristics. This data would be important for the CLIN1 mission of generating data needed for an IND-enabling activity.

	● The PepSeq assay to identify immunologic epitope targets may provide significant pre-clinical value because peptide information can lead to monoclonal antibody treatments. ● The application tried to address more work than they could do with the funds and time available. I recommend either focusing the study through a simple revision with what they could reasonably accomplish with the resources, or find additional support to strengthen the relationship to clinical outcomes.
No: 8	● The bench work is laid out in limited detail but is clear. Similar work will be underway at many other labs. ● The antibody characterization is outstanding. ● It is unclear whether the clinical study will be useful or not. Understanding the short timeline to submit this proposal, it is still lacking many details. The clinical trial outcomes, enrollment and statistics need to be fixed. ● There is concern regarding the power calculation. Management of type 1 and type 2 error will be immensely important. There is also an ethical question at play--if the lab identifies a clear signature of a very harmful pattern of immunity in CCP, how will that information be communicated back to Mayo and the FDA and/or potential participants? On a similar ethical note, they should not be excluding patients with decisional impairment (common among critically ill patients). ● The clinical data collection is not complete. Treatment dose and volume are needed. ● Control groups are needed. ● Follow-up is needed.
GWG Votes	Is the proposal feasible?
Yes: 10	● The characterization of CCP is feasible. ● The issues with clinical trial design seem fixable to make this proposal feasible. ● The rationale is strong. Description of the execution of the clinical component is weak. Concerns include: ● lack of sufficient statistical justification for the number of subjects ● lack of protocol details for the dose ● lack of predictable disease markers ● lack of sufficient infrastructure to support complexity including recipient subject recruitment ● The recruitment of donors relies on referring physicians to perform several labor intensive steps separated in time and involve referring potential donors to a website, later collecting a swab and/or blood, and later donating plasma. This is a tremendous amount of coordination that is not likely to succeed when left to referring physicians alone. ● The FDA guidance relies heavily on the gender of the donor (never pregnant females or females tested and negative for HLA antibodies for males) for the safety of the recipient. This study does not address handling of gender identification and donor eligibility in their online pre-screening process. ● Potential risks to participation do not address nasopharyngeal swabbing, which can cause discomfort and epistaxis.
No: 5	● The bench work seems feasible. ● The lack of important clinical details on a clinical project raises concerns for feasibility of the clinical aims: ● funding for sites needed ● data coordination needed ● emphasis on timeliness for data entry needed ● safety monitoring plan needed

Application #	DISC2COVID19-11817
Title (as written by the applicant)	Stem cell-based rapid identification of SARS-CoV-2 T cell epitopes and T cell receptors for therapeutic use
Research Objective (as written by the applicant)	We will identify SAR-CoV-2 T cell epitopes for vaccine development and specific TCRs for adoptive T cell therapy using a stem cell-based platform to generate specialized dendritic cells in vitro.
Impact (as written by the applicant)	New methods to rapidly identify T cell epitopes would greatly accelerate development of vaccines and TCR-based therapeutics, and in the setting of COVID-19 is an area of urgent unmet medical need.
Major Proposed Activities (as written by the applicant)	• Adaptation of hematopoietic stem cell-based cDC1 platform to SARS-CoV-2 • Capture and TCR sequencing of SARS-CoV-2 reactive T cells • Cloning of SARS-CoV-2 reactive TCRs and construction of a TCR reporter cell line library • Epitope mapping by peptide-MHC functional screen • Tetramer construction and convalescent validation cohort • Data dissemination and translational planning
Statement of Benefit to California (as written by the applicant)	The threat of the COVID-19 pandemic to the health of California citizens and the economy of the state is incalculable. While new treatments for established disease are vital, prevention of the viral infections is the only realistic solution to ongoing suffering and societal dislocation. Our proposed research builds on our ability to generate specialized immune cells in the lab from blood forming stem cells and to use them to discover the viral antigens that have highest potency for vaccines.
Funds Requested	$150,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 95

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	95
Median	95
Standard Deviation	3
Highest	100
Lowest	90
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• Identification of immunogenic T cell epitopes is a key requirement for effective vaccine design to treat COVID-19. The proposed project applies a novel, stem cell-based immune discovery platform to the simultaneous identification of SARS-CoV-2 T cell epitopes and their corresponding T cell receptor (TCR) sequences. • The proposed technology will likely result in TCR-T cell therapy candidate for COVID-19 viremia and related conditions. The proposed work will take advantage of technology developed by the PI for the generation of type 1 conventional dendritic cells (cDC1) from

	hematopoietic stem/progenitors cells and apply it to an immune discovery platform to model and capture T cell responses and T cell receptors (TCRs) against SARS-CoV-2 antigens in vitro. ● The expected outcome of the proposed work is the identification of novel TCRs that are specific for SARS-CoV-2 spike protein antigens, which can be useful for immune monitoring of infected and/or convalescent patients. Additionally, the work product will include the characterization of peptide/MHC multimers that can be used as diagnostics or for immune monitoring virus or vaccine responses. ● This is an excellent method to develop candidates for antigen epitope targeted T cell therapy which may produce both vaccines and T cell based therapies. ● Could lead to transformative diagnostics and cell therapies for COVID-19. ● Approach is relevant to potential vaccine and T cell therapies. ● This project could immediately impact the development of novel COVID-19 vaccines and therapies. ● The proposal provides a clear progression from discovery to validation and clinical translation. ● Excellent application.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	● The PI provides a strong and clear rationale for the use of stem cell derived cDC1 as an excellent platform for the presentation, identification and characterization of COVID-19 peptide epitopes to be used for the discovery of antigen reactive T cells and TCRs. ● This approach is based on the directed differentiation from human hematopoietic stem and progenitor cells (HSPCs) of endogenous-like cDC1 uniformly presenting the SARS-CoV-2 S antigen. The ability to generate cDC1 that process and present all available antigenic epitopes in a physiological manner may solve many of the obstacles facing existing epitope/TCR discovery approaches. ● The rationale is very sound and goes beyond the all-to-common computational approach to identifying T cell epitopes. ● The proposal offers a potential improvement over computational technologies. ● The preliminary data are derived from the PIs seminal work characterizing an in vitro system for the generation of human cDC1 and then showing how these cells provide an excellent platform for activation antigen specific T cells. ● The rationale is based on the PI's previous work and preliminary data demonstrates their ability to use this system to identify candidates for SARS-CoV-2 virus. ● The proposed work makes use of human hematopoietic stem/progenitor cells to generate, otherwise rare, cDC1s. ● The proposal is a great application of stem cell technology and immunology.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	● The project is well planned and designed in sequential manner, based on objectives and milestones. ● The proposal is very well thought out and well planned, with a specific targeted strategy. ● The project is crisply outlined and well aligned with the program announcement. ● The in vitro approach is straightforward and should yield results. ● The PI considers the use of convalescent samples to perform the T cell activation steps, but argues that these patients are know to suffer from lymphopenia and their T cells may be exhausted. These are good arguments, however, there is also the possibility that these patients would have memory T cells that would be highly reactive to the relevant immunodominant virus epitopes, which would represent an important cell target. ● The introduction claims other knowledge is "on a rudimentary understanding". This is probably too strong an indictment of the current state of understanding, and may be better phrased as "an incomplete understanding."
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 14	● This is likely to succeed. The team, timeline, facilities, and budget are all in place to complete this work in a reasonable timeline. ● The timeline is reasonable and feasible. ● The PI is leader in the field of hematopoietic lineage differentiation, having pioneered the generation of cDC1 from HSPCs, and has ample expertise to carry out the work. ● The PI has assembled an outstanding team to carry out the work. ● Great team with established technology.

	• The team is appropriately qualified for this type of work. Two staff members and PI would be sufficient to complete the project within one year with appropriate funding. • There is potential for a therapeutic candidate within 6-8 months.
No: 0	*none*

Application #	DISC2COVID19-11764
Title (as written by the applicant)	Identifying a lead compound for COVID-19 using high throughput screening with lung stem cell organoids
Research Objective (as written by the applicant)	We propose to use a lung stem cell based organoid to identify a new compound for COVID-19 by screening a library of FDA approved compounds that could be repurposed for COVID-19 infection.
Impact (as written by the applicant)	If successful, we will find a therapy to treat COVID-19 infection and prevent the lung complications that are so deadly.
Major Proposed Activities (as written by the applicant)	• Develop a drug screen in our COVID-19 infected lung organoid model • Run the drug screen for current FDA approved compounds that stop proliferation of COVID-19 in the lung organoid and identify which compounds work the best (hits) • Develop a secondary screen to find which of the hits from the primary screen also reduce death of the lung cells • Run the secondary screen to find which hits are best at preventing lung cell death and check which drug concentrations are the best at reducing viral proliferation for the hits • Analyze all the data from the primary and secondary screens and find the hit molecule that reduces viral proliferation and prevents the lung cells from dying and works well even at low concentrations.
Statement of Benefit to California (as written by the applicant)	COVID-19 has spread rapidly across California with over 15,800 cases being diagnosed and 372 deaths so far. The pandemic shows no signs of slowing in California and 53 out of 58 counties are affected. The economic impacts are also being felt all over California and the loss of jobs and incomes is staggering. The identification of a therapy to treat this virus would have a huge impact on saving lives, preventing severe infections and allowing people to return to their normal lives.
Funds Requested	$149,998
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 85

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	83
Median	85
Standard Deviation	5
Highest	86
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	4

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• The goal to identify small molecules through high-throughput screening (HTS) to inhibit SARS-CoV-2 infection is essential to treat COVID-19. • The proposal may find a new COVID-19 therapeutic compound using a relatively unbiased approach.

	• There is a fair chance that the proposed high-throughput screen may identify unique candidate molecules from the library of off-patent drugs that have activity against SARS-CoV-2. • The screening platform could identify a new compound that other companies fail to find. • This is a proposal to develop a lung organoid model for a screening. If successful, it may also aid in the discovery of a small molecule that could alter some of the effects of COVID-19 infection. • Because the screen focuses on approved drugs with expired patents, progression of a successful candidate to preliminary human trials should be straightforward, although the path by which such translation would be accomplished is not addressed specifically in this proposal. • Use of the stem cell-derived lung organoid system to conduct high-throughput screening of drug candidates for SARS-CoV-2 is unique, but it is not clear that it is necessary to identify such candidates.
No: 1	• It's not clear the proposed method is a superior way to screen compared to the many methods already available, and if not successful, there is little learned that advances the field. • The approach is novel, but I don't see that it is consistent with the direction and focus of CIRM.
GWG Votes	Is the rationale sound?
Yes: 12	• There is a clear need for antiviral drugs with activity against SARS-CoV-2. There is a strong scientific rationale for conducting a high-throughput screen using already approved drugs in the lung organoid system. • This a good approach and improving the lung organoid system for high-throughput screening may reveal some potential drugs. • Although it is likely other groups and companies are also testing a similar library of approved drugs, more swings at the plate are helpful. • The investigators clearly have experience with the lung organoid system, high-throughput screening in other systems, and in vitro cultivation and drug inhibition of SARS-CoV-2 in their institutional BSL3 facility. • There is no data to show that they can infect the lung organoids with SARS-CoV-2 or inhibit infection with putative antiviral compounds such as hydroxychloroquine in the lung organoid system (preliminary data are limited to Vero cells). • The lung organoid system depends on use of human progenitor cells. Although the lung organoid culture offers some unique advantages, is it necessary for screening a drug library? Would it be faster/more efficient to screen in typical 2-D cultures first, and then test lead compounds in their model?
No: 2	• The organoid model is not ready for utilization to make a timely impact. • The rationale for limiting the screen to the proposed compound list is not sufficient.
GWG Votes	Is the proposal well planned and designed?
Yes: 11	• The project is well-designed to meet expected program outcomes and identify a candidate ready for advancement into clinical trials. • A major strength is the plan to work with SARS-CoV-2 rather than pseudotyped virus. • The dosing range needs to be reconsidered. The concentrations selected for Milestone 4 may not be adequate/appropriate. For example, the EC50 for hydroxychloroquine is reported to be ~4 uM, and that of favirpiravir (now entering phase 2b trials) is ~60 uM.
No: 3	• The need to identify a single lead compound in Milestone 5 is limiting. Milestone 5 should be to rank and annotate all the compounds and publish all the data. If there are more good lead compounds than you can handle, get these out to other institutions that can test them. • The applicant proposes a relatively limited screening capacity of about 2,000 compounds. Given this limited throughput, consider including those compounds (in place of some of the default library compounds) that already have open-source computational, or expert, or literature, or clinical-anecdote evidence for COVID-19. Suggestions for drugs to test are rapidly evolving, so current best pre-approved drug choices could be got through open-source efforts such as https://www.academicdatascience.org/covid https://covid19-hpc-consortium.org/projects/5e86fdbc44c9d8007ff92161 (e.g., Rapid antiviral drug discovery for SARS-CoV-2) https://clic-ctsa.org/covid-19 (NIH & NCATS collaboration hub) • Additional data is needed to support proposed concentration selection for screening.
GWG Votes	Is the proposal feasible?
Yes: 12	• The investigator team is highly qualified to conduct the proposed experiments. • The team is well qualified with reasonable resources. • The team is well put together.

	● Adequate resources exist to accomplish the project goals. ● Significant delays could be entailed in achieving Milestone 1, without which the other milestones cannot fall into place. The 6-month timeline seems overly optimistic for achieving all 5 milestones and emerging with a lead candidate.
No: 2	● There is a lot of risk in the proposal and no easy way to mitigate them. ● There is concern regarding feasibility due to lack of infectivity data for organoids.

Application #	TRAN1COVID19-11793
Title (as written by the applicant)	COVID-19 Antiviral Therapy to Block Lung Stem Cell Injury and Associated Tissue Damage
Translational Candidate (as written by the applicant)	Berzosertib (VE-822), a safe drug candidate for treatment against COVID-19, will be investigated.
Area of Impact (as written by the applicant)	The outcome of the proposed studies will have a significant health benefit to COVID-19 affected patients.
Mechanism of Action (as written by the applicant)	Our drug candidate, Berzosertib, works as a treatment against COVID-19 by blocking a critical step in virus replication. Moreover, Berzosertib is a selective inhibitor of a key cellular enzyme ATR (ataxia telangiectasia and Rad3-related protein), which can result in disabling DNA repair pathway in damaged cells. Many viruses are known to hijack this pathway for efficient replication, thus inhibiting the DNA repair mechanism can block viral growth.
Unmet Medical Need (as written by the applicant)	Currently there is no treatment to limit the COVID-19 disease caused by SARS-CoV-2 virus, which is an unmet medical need.
Project Objective (as written by the applicant)	Plan to have Pre-IND meeting with FDA in 6 months
Major Proposed Activities (as written by the applicant)	• Testing Berzosertib drug dose course against SARS-CoV-2 using lung stem cell organoid model. • Assessing treatment effects of Berzosertib on reducing cell death and inflammation. • Determine time after infection at which the Berzosertib is still effective in lung organoid model.
Statement of Benefit to California (as written by the applicant)	Emergence of a highly-contagious novel coronavirus, SARS-CoV-2, precipitated the current health crisis with over 375 deaths and more than fifteen thousand confirmed cases in California. Development of effective antiviral treatment targeting COVID-19 can help benefit the affected patients and reduce the impact on California's health care system and economy.
Funds Requested	$349,999
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 80

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	80
Median	80
Standard Deviation	8
Highest	90
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	7
(1-84): Not recommended for funding	8

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• There are no approved therapeutics available for treating COVID-19 patients. This proposal identifies Berzosertib as a potent anti-SARS-CoV-2 drug and plans to further bring it to pre-IND stage. • Preliminary data of use of Berzosertib is compelling. They have a good plan to use the organoid model to establish efficacy. It is unclear whether the organoid model is infectable by SARS-CoV-2. • Good preliminary data with a logical target. • Moves a new antiviral compound towards application into COVID-19. • This would be a great opportunity to add to the tools in the arsenal for fighting COVID-19.
No: 4	• Initial lead candidate screen is limited to non-human cells and only 430 kinase inhibitors.
GWG Votes	Is the rationale sound?
Yes: 11	• The basis for Berzosertib mediated inhibition of SARS-CoV-2 replication is not well known. However, the applicant's rationale for the use of a FDA approved drug that showed promising results during phase 1/2 clinical trials to treat COVID-19 is sound. • "Pathway analysis" is a pretty vague term and does not allow a computational biologist to understand what was done. The pathway figure has no legend and has a jarring mix of irrelevant colors and shapes, so the message of the pathway figure does not come across clearly. Providing some sort of statistics and/or metrics as a result of the pathway analysis would help convince us this analysis actually adds something to the preliminary data. • Some of the concerns are addressed by the applicant in the response to the reviewers questions - these would need to be incorporated into the main proposal in a resubmission if they were to be best considered by the full panel. • After reviewing the response to a reviewer question, I am even more concerned about the pathway analysis. One of few compounds in the pathway that are not connected to anything is the compound that is proposed to be pursued. It does not seem to help the applicant's case. • It is closer than many applications to moving forward. • No concerns. • A slight concern about antiviral drugs targeting host cells, MOA not fully understood.
No: 3	• The organoid model is not tested. No evidence in the application that SARS-CoV-2 can infect the cells. • Over the last few years there has been interest in the repurposing of kinase inhibitors as broad spectrum antiviral agents; the proposed kinase family has not been considered. • No benchmark to evaluation of success in vivo, based on 2 log reduction in viral load in an in vitro system. • There is a presumption of an anticipated human dose based upon dose used in cancer indication.
GWG Votes	Is the proposal well planned and designed?
Yes: 11	• Yes, the project is well planned and designed. Berzosertib drug is already in phase 2 clinical trials and established a smooth transition from preclinical safety and efficacy study phases. • It is unclear if you can accurately measure 3 logs reduction in viral load with real time PCR. • Milestone 5 is probably not necessary (at this juncture). Coronavirus is a slow mutating virus. Even if resistance emerges, it could still be useful as part of a combination therapy, or to ablate the pandemic in early years or a subset of the population. • Rational design. • Concern about strategy and the focus on the organoid platform. • There is concern about the translatability.
No: 3	• I believe the screening in the organoid model is a good place to start, but need to show it will work in animal models. Not clear if the virus replicates in the organoid model. • No data to support infectivity of lung organoid cultures. • No consideration of in vivo confirmation in an in vivo animal model.
GWG Votes	Is the proposal feasible?
Yes: 11	• Considering this is a BSL-3 work, the timeline appears to be slightly insufficient. Despite this weakness, this is an excellent application. • Unclear if this will work in vivo. Animal studies would be needed to make sure it really works prior to moving forward. • Would be good to know if the applicants have had interactions with drug manufacturer. • Partnership with Merck needs to be clarified. • Concern about this drug being available from Merck.

No: 3	• Repurposing kinase inhibitor for anti-viral function is too far afield even with Merck's involvement. • It is risky, but again, not a lot of investment, so I think it's worthwhile. • Unclear whether they will be able to advance into clinic without ability to cross reference IND and/or leverage current CMC (i.e. GMP product supply).

Application #	DISC2COVID19-11779
Title (as written by the applicant)	Mesenchymal stem cell derived exosome repression of SARS-CoV-2
Research Objective (as written by the applicant)	We will develop a mesenchymal stem cell based therapeutic consisting of anti-SARS-CoV-2 exosomes that block virus infection or target virus infected cells to repress virus expression and disease.
Impact (as written by the applicant)	We will develop a mesenchymal stem cell based exosome therapy to treat COVID-19 disease caused by SARS-CoV-2.
Major Proposed Activities (as written by the applicant)	• Generate and assess siRNA containing mesenchymal stem cell (MSC) exosomes for repression of SARS-CoV-2 in vitro. • Develop and validate a single round infectious virus that expresses the full-length SARS-COV genome but with a luciferase/GFP replacing the spike gene for in vitro and in vivo work. • Generate and assess ACE2 virus receptor targeted MSC exosomes for blocking of SARS-CoV-2 and targeting virus infected cells. • Generate and assess ScFv protein S spike targeted MSC exosomes for blocking of SARS-CoV-2 and targeting virus infected cells. • Assess ACE2 expressing MSC exosomes for binding and blocking of SARS-CoV-2 in vitro and in vivo. • Assess spike ScFv directed siRNA containing MSC exosomes for targeting SARS-CoV-2 infected cells in vitro and in vivo.
Statement of Benefit to California (as written by the applicant)	This project will benefit the State of California by developing a therapeutic to treat COVID-19 disease by utilizing mesenchymal stem cells to generate a biological treatment that can either (1) target and soak up free virus or (2) target virus infected cells and inhibit virus expression, pathology and ultimately disease.
Funds Requested	$150,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 80

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	77
Median	80
Standard Deviation	10
Highest	87
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	11

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• The use of MSC and exosomes is very novel. Their methods target the SARS CoV-2 virus in several different ways which may prove very effective and harder for the virus to mutate around. • Exosome delivery of siRNA to inhibit COVID-19 is novel and has potential. • The use of exosomes have demonstrated to reduce severity of ARDS. Also, this group has developed a protocol that can be use to enrich RNAs, including siRNA, in the exosome. Also, they can direct the exosomes to specific cell targets by expressing different ligands in their surface.

No: 4	• The manufacturing of the product does not seem feasible to scale to high numbers of patients.
GWG Votes	Is the rationale sound?
Yes: 11	• The use of siRNA included inside the exosomes to inhibit SARS-COV-2 replication is highly novel. Expression of ACE2 to reduce the number of free virus can be an additional benefit of this technology. • The rationale that the expression of SARS-CoV-2 targeted RNAi containing exosomes from mesenchymal stem cells to inhibit SARSCoV-2 virus expression is sound. • The applicant has previous experience with HIV to support targeting of cells. • The exosomes themselves may have a beneficial effect, and the siRNAs may not be necessary. A clear control of plain MSCs is needed. • They plan to target at least three distinct regions of the SARS-CoV-2 RNA genome which should limit the potential for the SARS-CoV-2 to evolve resistance around the RNAi targeting. • They have tested their system of exosomes (in this case produced by HEK-293T producer cells, rather than MSC as proposed) and observed about 50% knockdown of the virus. It is unclear how difficult it will be to translate their system to MSCs, and if in their past work of 50% knockdown is biologically significant.
No: 3	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 6	• Experiments and milestones are very well laid out. • The studies are well planned.
No: 8	• This is an over ambitious project. The budget is very limited for the number of proposed experiments. • A better understanding of controls and comparisons that will be made to demonstrate signal would be useful. • Experimental details about dosing, controls, numbers are missing. • They propose to develop a single round infectious SARS-CoV-2 virus to aid in testing, but if not effective then test elsewhere with live virus. This may add significant time to the project and create set backs. • There are no available animal models to support efficacy assessments. • It is a bit of an overstatement to claim that an uncontrolled study of 7 individuals leads to a conclusion of "mesenchymal stem cell transfusions have been shown to be safe and effective." • In clinical studies, inhalation of an aerosol iRNA into the human respiratory tract has been used with some success and might be a simpler and faster route of approval for antivirals against respiratory viruses. • This a complex method and it may be difficult to manufacture the final product. • The technology seems over-engineered.
GWG Votes	Is the proposal feasible?
Yes: 7	• Very interesting concept, with a highly applicability not only to SARS-COV2 but other viruses. The use of MSC-derived exosomes can reduce possible secondary effects of the the use of live cells. • The studies are well planned. • The team appears to have the experience necessary to complete the studies. • Animal supply houses are currently restarting colonies of K18-hACE2 transgenic mice and it is not clear when the supply will be available or in what numbers. • Some work is dependent on a the BSL3 lab. It appears construction of a BSL3 lab at their institution has yet to begin. They do have a back up plan to work with another lab, but no indication of how it will be paid for. The letter of support from the backup lab is a bit vague and the logistics could be awkward and inefficient, particularly with current travel restrictions. • Budget will be very tight and no mention if additional funds are available.
No: 6	• Exosome delivery to the lungs is a major concern as to feasibility. • The timeline seems too ambitious. • No current capability for BSL3 experimentation. • Concern about BSL3 facility availability.

Application #	DISC2COVID19-11724
Title (as written by the applicant)	Rational Design of a SARS-CoV-2 Vaccine
Research Objective (as written by the applicant)	A vaccine against SARS-CoV-2
Impact (as written by the applicant)	There is a clear need for a vaccine to prevent the spread of the COVID-19 coronavirus that is effective, can be rapidly produced and can be scaled for worldwide demand
Major Proposed Activities (as written by the applicant)	• Identify structural regions of SARS-Cov-2 that can inhibit viral entry • Identify potential regions that can induce CD8+ T cell responses • Confirm which regions produce peptides that bind to human HLA Class I molecules • Confirm which peptides induce antibodies inhibit viral entry using hematopoietic and bronchioalveolar stem cells • Identify which peptides induce CD8+ T cells that lyse cells containing Spike protein from SARS-CoV-2
Statement of Benefit to California (as written by the applicant)	This research will result in a vaccine candidate that will protect California citizens from contracting COVID-19, allowing its people to interact freely and resume normal activities.
Funds Requested	$149,999
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 75

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	73
Median	75
Standard Deviation	8
Highest	95
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• Development of peptide vaccine with strong immunogenic properties is essential to develop effective vaccines against COVID-19. • Elegant proposal, but unproven, although exciting, technology. This would develop another type of vaccine to have in the tool kit. • New approaches to thinking about vaccine development are a welcome addition to the fight against COVID-19. • If successful, a new vaccine would be transformative.
No: 3	• Novel approach, but the technology has not been validated in an infectious disease model. • No relevance to stem cells.
GWG Votes	Is the rationale sound?
Yes: 6	• Interesting concept and technology.

	● The idea of using their technology to identify effective vaccination peptides is novel and sound. However, the rationale for the experimental approach to demonstrate the neutralizing antibodies (i.e. using CD34+ HSC or BASCs) is not clear. ● Is proteasome catalyzed peptide splicing (PCPS) a standard vaccine approach? The review panel was split on whether (a) since few people were doing it, there was evidence that it was "too far out" to invest in, or (b) it was a great investment because of its unique and innovative approach. It would greatly strengthen the application to provide a strong rationale for this approach, both in terms of preliminary data (predicting known epitopes in other well characterized viral systems) and in terms of published data. For example, the proposal did not cite "An Unexpected Major Role for Proteasome-Catalyzed Peptide Splicing in Generation of T Cell epitopes: is There Relevance for vaccine Development? Anouk C. M. Platteel et al, Frontiers Immunology." I recommend ciing as many articles supporting this as possible, especially if they are not from the applicant, and summarize this literature/data review in the application. ● There is a lack of modeling of known cases e.g. MERS, SARS, or currently known COVID-19 epitopes. Recommend showing data that the method works to identify known epitopes on MERS and SARS-CoV. That would help the panel have confidence that it could identify epitopes on SARS-CoV-2.
No: 8	● Preliminary data provided doesn't demonstrate if immunogenic peptides can be identified by their method. ● The applicant needs to do the in silico research on known epitopes to make the case that this approach would be relevant. ● Preliminary data does not show if the stem cells are ideal for testing, or even necessary. ● The technology seems to work, but the MHC 1 issues are concerning.
GWG Votes	Is the proposal well planned and designed?
Yes: 6	● There is no preliminary data provided to show that there are potential immunogenic peptides that can be identified by their method. ● There is the distinct possibility that the virus could mutate/recombine to become more virulent, though this is not considered a major concern for the Coronavirus group and current mutations rate data does not support this concern.
No: 8	● Peptides as therapies can be difficult. Here, they provide no information about the amount of peptide, route of injection, frequency and so on. ● The lack of investigation of the information in established relevant epitope studies is a major weakness. ● More data is needed regarding the applicability of the approach towards known SARS-CoV-2 epitopes. ● The plan to assess immunogenicity is limited by the current design. ● There is concern about the applicability to infectious disease, especially with respect to MHC class.
GWG Votes	Is the proposal feasible?
Yes: 9	● If successful, the milestones can be achieved within the specified time frame. ● It would be ideal to add a virologist to strengthen the proposal. ● They have tools and expertise to carry out the aims. ● It is technically feasible, but whether it would have any outcomes of interest is entirely speculative.
No: 5	● Providing initial preliminary data would strengthen the proposal.

Application #	TRAN1COVID19-11837
Title (as written by the applicant)	Development of Decidua Stromal Cells for the Treatment of COVID-19-induced Acute respiratory distress syndrome (ARDS) or any ARDS
Translational Candidate (as written by the applicant)	Placenta-Derived Decidua Stromal Cells (DSC)
Area of Impact (as written by the applicant)	COVID-19-induced Acute respiratory distress syndrome (ARDS) or any ARDS
Mechanism of Action (as written by the applicant)	DSCs were found to suppress alloreactivity and increase the frequency of Tregs. Several factors (e.g., IDO, PGE2, PD-L1, and IFN-γ), were found to be important for the suppression. DSCs constitutively expressed IDO, which appeared to be important for the induction of Tregs. In addition, DSC-induced down-regulation of the IL-2R, IL-8 and IL-6 can reduce further activation and proliferation of T cells.
Unmet Medical Need (as written by the applicant)	Current management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality. Based on our case-study testing, our therapy will offer treatment to these patients within minutes after the infusion.
Project Objective (as written by the applicant)	Complete CMC IND-enabling studies and submit IND
Major Proposed Activities (as written by the applicant)	• Complete assay transfer and qualification • Complete engineering and qualification runs • IND submission
Statement of Benefit to California (as written by the applicant)	Our proposed therapy (based on Decidua Stromal Cells) will be manufactured in California. The therapy will be available to patients with COVID-19 and should result in immediate relief of breathing symptoms.
Funds Requested	$350,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 70

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	65
Median	70
Standard Deviation	11
Highest	75
Lowest	30
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 5	• Decidua stromal cells (DCSs) have been shown to be safe in clinical trials conducted in Sweden, mostly in patients with GVHD. However, no evidence that this works on ARDS, only one anecdotal case. There is a positive response from the FDA to initiate clinical trials for GVHD and to discuss the use of DCSs for COVID-19. • Treating ARDS in COVID19 patients is a significant medical need. • If the therapy works, it would have the potential for impact. • Mechanism of action (MOA) of COVID-19 infection is not completely known. The proposed cell therapy provides potential to have general anti-inflammatory activity.

	• If it could shorten hospital stays and help the sickest patients, as proposed, it would have a major impact.
No: 9	• There is a relatively long time to potential societal benefit and the intervention is at a relatively late point in disease; so although it might work, may not be as high a priority for funding as other proposals that intervene at early stages of prevention and treatment. • The significance of this strategy is not high.
GWG Votes	Is the rationale sound?
Yes: 2	• Data in the proposal does not explain in detail the possible mechanisms by which DCSs can protect against COVID19-ARDS. The FDA positive response and literature suggest that the use of DCSs could have a positive effect on COVID-19 positive patients. • The rationale for testing DSCs as a potential therapy for ARDS is two-fold: a) that these cells have superior potent immunosuppressive properties compared to stem cells from other sources and b) have already been shown to be safe and therapeutically effective in clinical studies in acute and chronic GVHD, hemorrhagic cystitis, radiculomyelopathies and other severe inflammatory conditions.
No: 12	• The use of DSCs, a version of MSCs, will likely have the same effects as seen for MSCs in vivo. • The proposal includes statements that are not fully supported by the cited scientific publications. • Most of the data is based on one patient, but not at all clear if the improvement in the patient was due to the therapy. The patient had pulmonary issues not related to SARS-CoV-2 or similar. • There is a growing body of evidence that in well-controlled studies, MSCs or MSC-like cells do not demonstrate sufficient clinically meaningful benefit. • Mechanism of action is not clear. • The rationale is weak. The cells are proposed to be anti-inflammatory and 'allo-suppressive' but the link to ARDS and COVID-19 is weak. The bulk of the proposal is based on the fact that one cancer patient who received a transplant and then developed ARDS got better after a dose of DSCs. It is not clear if this patient might have recovered anyway. • There is not much supportive data related to COVID-19 or ARDS. In one place, the applicant states the cells are comparable to MSCs, but later acknowledges that in two randomized trials MSCs were safe but not more effective in ARDS compared to placebo.
GWG Votes	Is the proposal well planned and designed?
Yes: 6	• The transfer of the technology to produce GMP-grade DCSs is possible. The already initiated pre-IND discussion for the use of these cells in COVID-19 patients is a positive. • It is well planned and designed, but the preliminary data is too limited. • The project is low risk in terms of regulatory; they can likely meet the timelines.
No: 8	• It is unclear whether the applicant's claim is that MSCS are "naturally immune" to SARS-CoV-2, or that they release anti-inflammatory factors that suppress the cytokine storm, or both. It would seem that these two abilities would not necessarily go together, and might even be in conflict. • Not well planned and designed - these stem cells would have unknown function. • No data to adequately evaluate the plan.
GWG Votes	Is the proposal feasible?
Yes: 9	• If the cells are effective, as the investigators are proposing, this can be an important alternative. • The cell type is very near approval via FDA. • Translation of manufacturing protocols will come from Sweden. While never easy, very possible. • Previous FDA interactions provide pathway for acceptable manufacturing/product characterization. • There is concern that a clinical site has not been identified.
No: 5	*none*

Application #	DISC2COVID19-11729
Title (as written by the applicant)	Preclinical Development of An HSC-Engineered Off-The-Shelf iNKT Cell Therapy for COVID-19
Research Objective (as written by the applicant)	Allogeneic HSC-engineered iNKT (AlloHSC-iNKT) cells
Impact (as written by the applicant)	Treatment for COVID-19
Major Proposed Activities (as written by the applicant)	• Milestone 1. Production of the AlloHSC-iNKT cells • Milestone 2. Characterization of the AlloHSC-iNKT cells • Milestone 3. Delivery of the new therapeutic candidate
Statement of Benefit to California (as written by the applicant)	The novel SARS-CoV-2 is the cause of the coronavirus disease 19 (COVID-19) pandemic, which is responsible for over 780,000 cases and 37,000 deaths worldwide. There are 160,000 COVID-19 cases in the US, including over 7,000 cases in California. The proposed off-the-shelf allogeneic HSC-engineered iNKT (AlloHSC-iNKT) cell therapy, if successful, may provide a treatment and save lives of COVID-19 patients at California.
Funds Requested	$149,998
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 70

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	67
Median	70
Standard Deviation	6
Highest	75
Lowest	55
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 6	• The strengths of the project: good technology, very experienced team of researchers, the product development and process development has been done already and the first generation of iNKT product was used in an oncology clinical trial. • The major concern is lack of evidence for potential anti-viral effects of iNKT cells in acute respiratory infection. • The proposed stem cell-based therapeutic product would address the unmet medical need of suppressing hyper-inflammatory responses observed during COVID-19 infection. • The proposed project likely will result in a therapeutic candidate for COVID-19. The unmet medical need in COVID-19 is huge. There is no proven therapy currently available for this condition. However, the proposed technology is unlikely to result in a favorable clinical outcome.
No: 7	• The proposed work aims to generate allogeneic invariant natural killer T (iNKT) cells from hematopoietic stem/progenitor cells, which could be given to COVID-19 infected patients in the hopes of a beneficial outcome. Although this is a laudable goal, it is highly unlikely to succeed and difficult to see it being completed within the one year timeframe. • The use of allo-HSC-derived iNKT cells for the treatment of COVID-19 patients, even assuming these cells would help to target virally infected cells, may succumb to host-vs-

	graft rejection since it is expected that the lung/upper respiratory area would be highly inflamed with high levels of interferons, which would lead to the increased expression of allogenic HLA class-I and class-II molecules on the iNKT cells marking them for removal by the host T cells, and further exacerbate the clinical outcome. ● A major strength is that the iNKT cell manufacturing is pretty well established. However, it is unlikely that the iNKT cells will beneficially impact COVID-19 patient outcomes. ● It doesn't appear that these engineered iNKT cells can specifically target and eliminate SARS-CoV-2 virus or infected cells without creating other issues. ● The impact of NK cells may be less relevant for infectious disease vs. oncology.
GWG Votes	Is the rationale sound?
Yes: 2	● iNKT cells can target SARS-CoV-2 infected cells and reduce lung injury.

No:
11
	● Based on literature references and preliminary work presented in the proposal, it is not convincing that HSC-derived engineered iNKT cells will efficiently and selectively eliminate SARS-CoV-2 infected cells without excessive activation of immune reaction.
	● The rationale for the project is mostly sound, ie., is based on solid preliminary data showing the generation of iNKTs from HSCs. However, the failure to consider the in vivo exposure to high levels of interferon signals makes the use of an allogeneic cell product not likely to work, and a major flaw of the approach.
	● An interesting approach, but given the highly inflamed lung environment in the patient, this type of treatment could induce a graft-vs-host rejection.
	● The PI does consider the use of a CRISPR based approached to remove B2M to eliminate MHC-I expression, plus the addition of a conserved HLA-E gene to counter NK cell targeting. This approach further complicates the initial genetic manipulation of the HSCs and fails to eliminate the potential expression of all MHC-II expression upon INF exposure.
	● The use of TCR-transduced HSCs differentiated into iNKT cells could be an attractive approach for immune-oncology applications, as already funded by CIRM.
	● A sound rationale for using iNKT cells is needed.
	  ● There is little data presented to support the hypothesis that iNKT cells can clear infected cells.
	  ● There is also not much suggestion in the literature that iNKT cells can play a role in clearing virus infected cells.
	● There does not appear to be a strong rationale for this cell type playing a role in viral clearance.
	● Unlike cancer, the data to support iNKT cell therapy (including any literature references) as efficient therapeutic anti-viral agent is lacking.
	● COVID-19 infections have very complicated biology, but T cells will be needed; too many NK cells could cause dysregulation.
	● The role of T cells in this disease is not yet clear - the timing could be either beneficial or detrimental.

GWG Votes	Is the proposal well planned and designed?
Yes: 4	● No weaknesses noted.
No: 9	● The PI has ample expertise in the field and has developed the technology for generating iNKT cells in vitro using the Dll4/VCAM1 approach published by Zandstra (although not cited). The PI is an emerging leader in the field of immune cell engineering. ● The PI points out pitfalls, but the solutions would likely make the project even less likely to be completed within the proposed timeframe, and fails to consider the potential expression of allo MHC-II. ● The ongoing viral response in the host needs to be considered by the applicant. ● The most critical part is to demonstrate preliminary effects of iNKT cells on SARS-CoV-2 and SARS-CoV-2 infected cells. In this regard, it is unclear why researchers would not take aliquots of cryopreserved iNKT product, prepared for clinical trial in oncology and perform proposed in vitro assays with SARS-CoV-2. This could be done relatively quickly without getting into manufacturing improvements and runs to generate new batches of the product. ● Suggest side by side comparison with viral specific T cells. ● The proposed pre-clinical models could be more relevant. ● The proposed animal model is mimicking design for cancer proof of concept, and it is unclear whether this model will be feasible/relevant for infections diseases in general and COVID-19 in particular. ● No alternatives or work arounds are presented. Timeline may be too short.
GWG Votes	Is the proposal feasible?

Yes: 9	• The team and the budget are appropriate, but a very tight time schedule to complete the work. • Experienced team. • The team is highly qualified and appropriately staffed, and have access to all necessary resources in order to perform proposed work. • If the xenograft NSG mouse model is not established and group has no experience, it could take longer than 12 months and exceed the budget.
No: 4	• The PI has assembled a superb advisory team, and an outstanding group of collaborators. • The project is clearly outlined, but unlikely to meet the timeline, and may not achieve the stated goals for the reasons pointed out above. • The milestones are logical in how they are presented and how the project would move forward. The proposed timeline may be difficult to achieve. • Too ambitious for the amount of the award. • A major concern is that graft vs. host could conceivably be higher in a hyperimmune state of COVID-19 compared to cancer.

Application #	DISC2COVID19-11763
Title (as written by the applicant)	Development of TMPRSS2 antibody as an antiviral treatment for SARS-CoV-2 (COVID-19)
Research Objective (as written by the applicant)	We want to investigate if TMPRSS2 antibodies can be used as therapeutic drugs against SARS-CoV-2 infection on alveolar epithelial type 2 cells, the stem cells in the lung.
Impact (as written by the applicant)	If successfully achieved, we will have a therapeutic drug for COVID-19 for which currently no treatment and vaccine available.
Major Proposed Activities (as written by the applicant)	• Test if TMPRSS2 antibodies are toxic to lung cells. • Test if TMPRSS2 antibodies can stop SARS-CoV-2 infecting lung cells. • Test if TMPRSS2 antibodies can stop SARS-CoV-2 making more new virus for spreading. • Test if TMPRSS2 antibodies can decrease the level of TMPRSS2 protein on cell surface. The less TMPRSS2 on cell surface, the less enzyme the SARS-CoV-2 can use to enter cells. • Test if TMPRSS2 antibodies can block enzymatic activity of TMPRSS2. The less enzymatic activity, the less SARS-CoV-2 can enter cells.
Statement of Benefit to California (as written by the applicant)	There is currently no vaccine and treatments available for COVID-19 and California currently is the 4th state with most confirmed cases. The development of vaccines might take longer than a year. Antivirals, on the other hand, are likely to be developed and approved faster and are potential treatments for the COVID-19. Here we proposed to investigate the possibility of developing TMPRSS2 antibodies as antivirals for SARS-CoV-19. If successful, we will have a potential treatment for COVID-19.
Funds Requested	$150,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 65

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	68
Median	65
Standard Deviation	6
Highest	85
Lowest	65
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 8	• Identifying an antiviral that blocks SARS-CoV-2 entry is critical to treat COVID19. • More biology would be discovered with this system. • There is currently a small molecule in the clinic that inhibits this enzyme.
No: 6	• Organoid model has not been shown to express the protein, key to show this. Use of the pseudotype model is fine but should show infection of the cells. • At best the proposal will identify several mouse antibodies which may block viral entry into human cells.
GWG Votes	Is the rationale sound?

Yes: 6	• The proposal is based on the rationale that TMPRSS2 is essential for virus entry, and inhibiting TMPRSS2 will stop virus entry and replication. • The proposal cites two references "An In vivo model showed that lack of TMPRSS2 in the airway reduces the severity of lung pathology after infection by SARSCoV and MERS-CoV, suggesting the importance of TMPRSS2 in coronaviruses pathogenesis13,14." Neither reference 13 or 14 mentions SARS nor MERS.
No: 8	• Thought on how to translate the antibody into human studies is needed. How would the antibody be delivered? Potential toxicities need to be considered as there is autoimmune disease potential. • The toxicity on host cells needs to be considered. • There is no evidence that the lung organoid is a good model to test their ideas. • There are currently no known antibodies for infectious disease that target epitopes other than the virus or host cell receptor. • Additional consideration for lead optimization and/or what characteristics of the antibodies is needed.
GWG Votes	Is the proposal well planned and designed?
Yes: 6	• The proposed milestones suggest a lack of urgency. It's not clear how many of the experiments are necessary to quickly advance to a novel therapy ready for the clinic. • More consideration for the translation of this approach into a therapeutic is needed.
No: 8	• More thought is needed on how the antibody and therapeutic product would work. • The proposal lacks a well designed plan. The use of organoid cultures does not seem to be the best fit to expeditiously move the antibody into the clinic. • It is not clear how a lead candidate will be selected and how these antibodies would humanized. • It is unclear how a lead candidate antibody will be selected. • The murine antibody would most likely have to be humanized.
GWG Votes	Is the proposal feasible?
Yes: 11	• Small chance of success. • As written, it is feasible and the team is well qualified to run these experiments. • Good team.
No: 3	• The proposal appears to be ambitious and this reviewer has reservations that it can be completed in 12 months. • It is unclear how this mAb would be used clinically.

Application #	DISC2COVID19-11759
Title (as written by the applicant)	Therapeutic strategy for COVID-19 associated acute cardiac injury using hPSC modeling approaches
Research Objective (as written by the applicant)	A human stem cell based screening strategy will be utilized to identify FDA approved drugs that protect against acute heart injury in COVID-19, that is the main cause of death in these patients.
Impact (as written by the applicant)	The proposed studies will identify a FDA approved drug that can be repurposed to alter wound healing and inflammation and can be used for treating heart injury in COVID-19.
Major Proposed Activities (as written by the applicant)	● Screen drugs (that we have already identified to benefit acute cardiac injury) against human stem cell derived cardiac muscle cells exposed to SARS-CoV-2 ● Identify drug amongst above which rescues cell death of both human stem cell derived cardiac muscle cells and cardiac non-muscle cells ● Identify lead candidate amongst above that has the least toxicity ● Determine whether lead candidate protects against acute cardiac injury in a pre clinical murine model of SARS-CoV-2
Statement of Benefit to California (as written by the applicant)	Acute cardiac injury in COVID-19 is one of strongest predictors of fatality in this disease. Currently there are no therapies for COVID-19 induced acute cardiac injury which is thought to occur via direct viral injury and a dysregulated immune response. By identifying a FDA approved drug that can be used for this purpose, thousands of COVID-19 patients in California stand to benefit immediately from this proposal.
Funds Requested	$149,998
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: --

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 3	● It is not clear if the majority of COVID-19 patients that died exhibit acute cardiac injury.
No: 10	● The drug would not likely have acute effects, but may spare cardiac tissue over a longer term and prevent heart failure down the road. ● There are currently no data to suggest that this is an appropriate target for COVID-19. ● The approach is not very relevant to acute COVID-19 heart failure.
GWG Votes	Is the rationale sound?
Yes: 1	*none*

No: 12	• The rationale that acute cardiac injury is a #1 risk factor is based on one study. The rationale requires a greater body of evidence. • The targets do not seem compelling. It's not clear that ENPP1 is a valid target in this setting. • There is no strong evidence that intervention will impact acute cardiac changes in COVID-19. • They present good evidence that inhibition of ENPP1 will spare cardiac tissue with ischemia, but no evidence if this is the same pathway for viral infections. • The murine model may not mirror human cardiac model. • The ENPP1-AMP axis may not be the mechanism of COVID-19 injury. • There is no evidence that this alters mortality rates in animals. • The need to find a usable drug to intervene in this axis may not be possible. • The acute benefit to patients is not clear, perhaps this would help in a chronic setting of repairing injured tissue.
GWG Votes	Is the proposal well planned and designed?
Yes: 3	*none*
No: 10	• Lots of redundant tests, why test in both cardiac cells and organiods? Why not move directly to mouse models? • What is the dosing scheme? The proposed timing of the dose would not be similar to what is possible clinically. • Prioritization for consideration of assessment in animal model of disease is recommended. • Establishing the iPS cells is not discussed. It could present many challenges and be lengthy.
GWG Votes	Is the proposal feasible?
Yes: 3	• No weakness noted.
No: 10	• The 1yr timeline seems impossible. • The iPSC work seems too difficult to move forward right now. • Getting fibroblasts from patients and generating iPS cells was not given thorough discussion. • The timing to support production of cardiomyocytes does not seem to have been considered. • The proposed animal models may not be available for some time. • The PI has significant time over load.

Application #	DISC2COVID19-11755
Title (as written by the applicant)	Nebulized mesenchymal stem cell therapy for COVID-19 patients
Research Objective (as written by the applicant)	Mesenchymal stem cells can help treat lung diseases, including COVID-19. Here, we are developing a technology that can deliver encapsulated stem cells localized to the lung using a nebulizer.
Impact (as written by the applicant)	We considered a technique that can localize and deliver stem cells above the effective concentration in the lung without using more cells than necessary to treat COVID-19 patients.
Major Proposed Activities (as written by the applicant)	• Development of inhalable microparticle generating microfluidic device • Development of biocompatible polymer for inhalable cell-laden microparticles • Long-term viability and functionality assessment of mesenchymal stem cell-laden microparticles • Viability assessment of nebulized mesenchymal stem cell-laden microparticles using commercialized nebulizer • Evaluation of bioactive properties of nebulized mesenchymal stem cell-laden microparticles • Assessment of mesenchymal stem cell-laden microparticle delivery to bronchial-ends and alveoli using ex vivo model
Statement of Benefit to California (as written by the applicant)	More than one million infected people and more than 65,000 died worldwide due to COVID-19. In California, as of April 3, more than 14,000 people infected and more than 320 people died because of COVID-19, but still it is increasing. Once localized pulmonary stem cell delivery to the lungs for COVID-19 patients becomes possible, the development of therapeutics will be accelerated by the biomedical laboratories located in CA areas, ultimately returning the health benefits of multiple CA citizens.
Funds Requested	$149,993
GWG Recommendation	(1-84): Not recommended for funding

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GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 3	• Virus induced inflammation is a significant determinant of the disease outcome. Avenues to reduce such hyperinflammatory responses are critical to provide host protection and increase survival.
No: 10	• Delivery of fluids and microparticles into the lung of patients with ARDS can have negative consequences for the patient. • Adding nanoparticles in patients with a pathologic lung is a fatal flaw.

	● A major concern is potential impact of directly administering a particulate including added volume in subjects with acute pulmonary disease. ● There is no evidence that MSCs are beneficial in acute lung disease, so no reason to believe a different delivery system will be beneficial.
GWG Votes	Is the rationale sound?
Yes: 2	● MSCs moderate a variety of inflammatory responses and is based on sound preliminary data.
No: 11	● Preliminary data does not support the hypothesis that IT delivery is better than IV in ARDS patients. ● Preliminary studies do not demonstrate that MSCs are not affected by encapsulation. ● Putting materials into the lungs of COVID-19 patients makes no sense. ● Two risky events must occur for success: 1. Mesenchymal Stem Cells work 2. Biopolymer coating makes them work better. It would be more conservative to study only one risky hypothesis in a proposal of this scope and funding. ● Preliminary data is very poor. ● MSC may be useful in the future for a chronic lung disease.
GWG Votes	Is the proposal well planned and designed?
Yes: 3	● The impact of nebulization of MSCs is not well established. ● The strength of the proposal is systematic development of a novel delivery system for MSCs which may be relevant to other diseases.
No: 10	● Some of the experiments like viability, bio-distribution are very naive and require better design. ● To put more materials in a compromised lung seems like a bad idea.
GWG Votes	Is the proposal feasible?
Yes: 2	● Encapsulation of MSCs and delivery by aerosol can be possible. However, there is no evidence that supports the need to develop this technology.
No: 11	● There is not sufficient data to support likelihood of success for the proposed milestones. ● Much work is needed.